Solution Structures of Glycine-Arginine Dipeptide Repeats and their complex with a deoxyribonucleic acid, as Studied by Small-Angle X-Ray Scattering and Molecular Dynamics Simulation

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Segments of abnormal dipeptide repeats (DPRs) are often found in the gene chromosome 9 open reading frame 72 (C9ORF72) in the patients of familial frontotemporal dementia (FTD) (a progressive disorder of the brain) and amyotrophic lateral sclerosis (ALS) (muscles decreasing in size, resulting in difficulty in speaking, swallowing, and eventually breathing), as a signature of the deseases. Such dipeptide repeating of 10 to 1000 times can be found in the brain or spinal cord of the patients, including poly Glycine-Arginine $(GR)_n$, poly Glycine-Alanine $(GA)_n$, poly Glycine-Proline $(GP)_n$, poly Proline-Arginine $(PR)_n$, and poly Proline-Alanine $(PA)_n$, in contrast, only 2 to 25 times can be found in normal human being. In proposed pathogenesis mechanisms of DPRs, GR DPRs are observed both in the nucleolus and within the cytoplasm, and are presumed to be capable of penetrating nuclear pores; moreover, they have an opporunity to adsorb DNA or RNA to cause cell toxicity. In this study, we used synthetic $(GR)_{25}$ DPRs and $(AC)_3$ single strand DNA (ssDNA) as a model system to examine their interactions and complex conformation via integrative HPLC/SAXS/UV-Vis absorption/Refractive index measurements in one sample elution. Integrative analysis of the UV-Vis/RI data reveals 1:1 association ratio of $(GR)_{25}$ DPRs and $(AC)_3$ ssDNA. Furhter molecular dynamics simulation captures a metastable conformation that can describe the corresponding SAXS data of the complex. In which model, the helical structure of $(GR)_{25}$ DPRs is partially melt for embracing contact with the ssDNA. The revealed complex conformation may be of hints on the cell toxicity of GR DPRs.